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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/727,779 | 12/03/2003 | Shea N. Gardner | IL-11191 | 7079 |

7590 03/29/2007

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| EXAMINER | |
|---|---|
| BERTAGNA, ANGELA MARIE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1637 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/29/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/727,779 | GARDNER ET AL. | |
| | Examiner | Art Unit | |
| | Angela Bertagna | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 13-17* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## FINAL REJECTION

### *Status of the Application*

1. Applicant's response filed January 4, 2007 is acknowledged. Claims 1-11 and 13-17 are currently pending. Claims 11 and 13-17 were amended, and claim 12 was canceled. Claims 1-10 are withdrawn from consideration as being drawn to a non-elected invention.

### *Priority*

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 10/394,337 and Provisional Application No. 60/428,579, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, neither application provides support for the instant claims 16 and 17, where the method is applied using n-mers of a size n+1, n+2, etc (claim 16), and where the

method is applied using oligos in multiple reading frames (claim 17). For claims 16 and 17, the filing date of the instant application (December 3, 2003) has been used for prior art purposes.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites "arraying ... fragments into groups." It is not clear whether the step intends to purify/separate actual DNA fragments into groups (*e.g.*, into different tubes, parts of an array, *etc.*) or "virtually" array fragments by using a computer program. As the relationship between the method steps is not clear, claims 11-17 are indefinite.

### *Claim Rejections - 35 USC § 102*

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 11 and 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Evans (US 2003/0087238 A1; cited previously). This pre-grant publication was filed August 2, 2001.

Regarding claim 11, Evans discloses a method of producing a DNA molecule of user-defined sequence (see for a general description the abstract and paragraph 6) comprising:

(a) pre-selecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into fragments of defined size (see Figure 3 and paragraph 58)

(b) arraying the fragments of defined size into groups (paragraph 58 and Fig. 3; see also paragraphs 82 & 132 where fragments of defined size are taught)

(c) separating the DNA sequence segments temporally (paragraph 58 where Evans teaches sequential addition of the segments)

(d) assembling the groups into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (paragraphs 58 and 68 teach assembly using a polymerase; paragraphs 38 and 93-98 teach assembly by PCR, which inherently comprises parallel synthesis and shuffling using a DNA polymerase)

wherein the step of separating the DNA sequence segments occurs temporally (see paragraph 58) and the step of assembling the groups into double-stranded DNA molecules of pre-determined base pairs is accomplished by adding the DNA sequence segments gradually, in sequence order (paragraph 58).

Regarding claim 13, Evans teaches that the DNA segments are added gradually, in sequence order (paragraph 58). Evans further teaches that the sequential addition minimizes

errors (paragraph 66) and that computational techniques may be use to optimize (minimize errors) in the entire method (paragraph 178).

Regarding claims 14 and 15, Evans teaches that the multiplicity of DNA segments comprise n-mers, where n is an even or odd number. Specifically, Evans teaches numerous examples of oligonucleotides with an even and odd number of base pairs, for example 15 and 16 mers (see paragraph 53).

6. Claims 16 and 17 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Evans (2003/0087238 A1; published May 8, 2003; filed August 2, 2001; cited previously). As noted above, claims 16 and 17 have not been granted benefit of the earlier filing date of the previously filed provisional and non-provisional applications, but rather the instant application filing date of December 3, 2003.

Regarding claim 16, Evans teaches that the oligonucleotides may be different lengths (paragraph 53). Evans further teaches examples of oligonucleotides with lengths of 15 (n), 16 (n+1), 17 (n+2), etc (see paragraph 53).

Regarding claim 17, Evans teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Evans teaches variation of the oligo length and overlap between the fragments (paragraphs 53 and 54). These DNA fragments inherently comprise multiple reading frames.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 11, 13-15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selifonov et al. (WO 00/42560; cited previously) in view of Evans (US 2003/0087238 A1; cited previously).

Selifonov discloses a method of making polynucleotides having user-defined characteristics (see for a general description, pages 3-6 "Summary of Invention" and also page 9, lines 23-31).

Regarding claim 11, Selifonov discloses a method of producing a DNA molecule of user-defined sequence comprising:

(a) pre-selecting a multiplicity of DNA segments that will comprise a user-defined DNA molecule by using computational techniques to virtually break the DNA molecule into fragments of defined size (page 14, lines 20-29; see also page 21, lines 12-22)

(b) arraying the fragments of defined size into groups (page 14, lines 27-30, where Selifonov teaches that the fragments may be left with the parental strands or transferred to a new population. Selifonov also teaches formation of new populations; see also page 21, lines 14-15 and lines 23-30, where sets are combined)

(c) separating the DNA sequence segments temporally (page 22, lines 4-19, where Selifonov teaches variation of the composition of fragments in the recombination reaction and/or performing multiple recombination reactions. This is a temporal separation of the DNA segments)

(d) assembling the groups into double-stranded DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase to produce the DNA molecule of user-defined sequence (page 21, line 23 – page 22, line 13).

See also Figures 4A-D for a flow-chart depiction of the method of Selifonov.

Regarding claims 14 and 15, Selifonov teaches that the multiplicity of DNA segments comprise n-mers, where n is an even or odd number. Specifically, Selifonov teaches the use of DNA segments (or fragments) in the range of 10-20 nucleotides or more, 20-40 nucleotides or more, 40-60 nucleotides or more, 60-100 nucleotides or more 100-150 nucleotides or more, etc (page 6, lines 8-10) and further teaches variation of the oligo length (page 33, lines 5-6), thereby anticipating oligo lengths with an even or odd number of bases. Selifonov further teaches a

specific example of oligos with a even number of bases (page 70, lines 18-19, where 40-mers are taught).

Regarding claim 17, Selifonov teaches that the multiplicity of DNA fragments comprises oligos in multiple reading frames. Specifically, Selifonov teaches variation of the oligo length and overlap between the fragmens (page 33, lines 1-6). These DNA fragments inherently comprise multiple reading frames.

Regarding claims 11 and 13, Selifonov teaches computational modeling in an effort to minimize reassembly errors (see for example, page 10, lines 26-33). However, Selifonov does not explicitly teach sequential addition of DNA segments in the reassembly process.

Evans teaches a method of synthesizing a user-defined nucleic acid sequence that anticipates the instant claims 11 and 13-17, as discussed above.

Regarding claims 11 and 13, Evans teaches that addition of the oligonucleotides in a sequential order (optimized by computational modeling) minimizes reassembly errors (see paragraphs 58, 66, and 178). Specifically, Evans stated, "The sequential polynucleotide assembly methods of the invention further reduce the error rate observed with methods that require hybridization of pools of large numbers of oligonucleotides" (paragraph 66). Evans further stated, "The sequential polynucleotide assembly methods of the invention eliminate the need for purification and allow for systematic assembly of identical sized double-stranded or single-stranded oligonucleotides" (paragraph 66).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the *in silico*-optimized sequential addition of DNA fragments

taught by Evans in the nucleic acid synthesis method of Selifonov. Evans expressly taught the advantages of sequential addition of oligonucleotide segments in sequence order, namely: (1) a reduction in the assembly error rate, (2) elimination of the need for an extra purification step and (3) parallel synthesis of identical-sized nucleic acids (see paragraph 66 and above). An ordinary practitioner would have been motivated by these teachings of Evans to sequentially add the fragments to the reassembly reaction in sequence order in order to improve the accuracy of the reassembly reaction, eliminate the need for further purification (thereby improving the speed and efficiency of the process), and obtain the ability to synthesize in parallel multiple, identically-sized nucleic acids. Thus, the method of the instant claims 11, 13-15, and 17 is prima facie obvious over Selifonov in view of Evans.

9. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selifonov et al. (WO 00/42560; cited previously) in view of Evans (US 2003/0087238 A1; cited previously) and further in view of Murphy et al. (USPN 6,994,963; cited previously).

The combined teachings of Selifonov and Evans result in the method of claim 11, as discussed above.

Selifonov teaches variation of DNA segment lengths and the use of a set of DNA segments comprising fragments of different lengths (see page 6, lines 8-10 and page 33, lines 1-6). However, Selifonov does not explicitly teach fragments of n+1, n+2, etc.

Murphy teaches a method of nucleic acid recombination. Briefly, the method of Murphy comprises primer extension and cleavage to create an "extension ladder" (column 4, lines 9-16)

followed by recombinatorial synthesis to produce a mutagenized or chimeric nucleic acid (column 6, lines 34-40).

Regarding claim 16, Murphy teaches that the "extension ladder" (a collection of DNA segments) may comprise sequences of different length, specifically, sequences different by one nucleotide increments (i.e. n, n+1, n+2, etc) (see column 6, lines 49-56). Regarding the differently sized sequences, Murphy stated, "Furthermore, the present invention may use a complete library of nucleic acid extension products that differ in length by a single base. As a result, recombinatorial mutagenesis results in recombined sequences with potential crossover points at every single nucleotide in a nucleic acid sequence" (column 3, line 66 – column 4, line 4).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize DNA fragments differing by one nucleotide in length (n, n+1, n+2, etc) in the recombination method resulting from the combined teachings of Selifonov and Evans, since Murphy expressly taught that such a fragment pool resulted in "recombined sequences with potential crossover points at every single nucleotide in a nucleic acid sequence" (column 3, line 66 – column 4, line 4). The ordinary practitioner of the method resulting from the combined teachings of Selifonov and Evans would have been motivated by the teachings of Murphy to utilize the above length-diverse fragment pool in order to maximize the diversity of the resulting recombined/reassembled sequences, thereby improving the method's ability to generate nucleic acids encoding proteins with improved functional properties.

***Response to Arguments***

10. Applicant's arguments, see pages 5-6, filed January 4, 2007, with respect to the rejection of claims 11-17 under 112, 2nd paragraph have been fully considered and are persuasive, in part. Applicant's amendment to claim 11 clarifies the issues raised previously regarding the terms "fabricating" and "to break....sequence into fragments". However, Applicant's amendment does not address the issue of "arraying". As noted previously and reiterated above, the phrase "arraying said fragments of defined size into groups" renders claim 11 indefinite, because it is unclear whether this step is intended to encompass virtual (i.e. *in silico*) arraying or physical arraying via transfer among sample tubes, etc. Applicant argues that the amendment of claim 11 to recite "to virtually break said user-defined sequence into fragments of defined size" resolves the issue of the clarity of the arraying step (page 7 of the response). This argument was not found persuasive, because it remains unclear whether or not the arraying step occurs *in silico* or *in vitro*. Therefore, the rejection of claims 11-17 under 112, 2nd paragraph is maintained.

Applicant's arguments, see pages 6-7, filed January 4, 2007, with respect to the rejection of claims 11, 14, 15, and 17 under 102(b) as anticipated by Selifonov et al. have been fully considered and are persuasive. Selifonov does not teach all of the elements of amended claim 11, and therefore, this rejection has been withdrawn.

Applicant's arguments filed January 4, 2007, regarding the rejection of claims 11, and 13-15 under 102(e) and the rejection of claims 16-17 under 102(a) and 102(e) as anticipated by Evans have been fully considered, but they are not persuasive. Applicant argues that Evans does not teach all of the elements of amended claim 11 (see page 7 of the response). This argument was not found persuasive, because as discussed above, Evans teaches all of the limitations of

amended claim 11. Regarding claim 11, Evans teaches that the reassembly process can be conducted using PCR (see paragraphs 38 and 93-98 above). Reassembly PCR is inherently a parallel synthesis reaction that comprises DNA shuffling and utilizes a DNA polymerase. Also, Evans teaches sequential addition of the DNA fragments during the reassembly process (paragraph 58). Therefore, Evans teaches all of the limitations of claim 11, and the rejections are maintained.

Applicant's arguments filed January 4, 2007, regarding the rejection of claims 12 and 13 under 103(a) as obvious over Selifonov in view of Evans, have been fully considered but they are not persuasive. Applicant argues that the combination of Selifonov and Evans does not result in the method of the claims as amended (see page 9 of the response). This argument was not found persuasive, because as discussed above, Selifonov teaches all of the elements of amended claim 11 except sequential addition of DNA sequence segments during assembly. Evans supplies this teaching and additionally provides express motivation for incorporating sequential addition into the method taught by Selifonov (see paragraphs 58, 66, and 178 cited above). Therefore, the combined teachings of Selifonov and Evans result in the method of claims 11, 13-15, and 17. This rejection is maintained.

Applicant's arguments filed January 4, 2007, regarding the rejection of claim 16 under 103(a) as obvious over Selifonov in view of Murphy, have been fully considered have been considered but are moot in view of the new ground(s) of rejection.

Regarding the obviousness-type double patenting rejection of claims 11 and 14-16 over claims 27 and 29-32 in co-pending application 10/394,337 in view of Evans, the terminal disclaimer filed on January 4, 2007 disclaiming the terminal portion of any patent granted on this

application which would extend beyond the expiration date of any patent granted on Application No. 10/394,337 has been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly, the obviousness-type double patenting rejection has been withdrawn.

***Conclusion***

No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
March 21, 2007

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
3/23/07